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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/489,101 | 01/21/2000 | Ali O. Gure | L0461/7073(JRV) | 5361 |

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| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | 17 |

DATE MAILED: 10/17/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/489,101 | Applicant(s) GURE ET AL. | |
|---|---|---|---|
| | Examin r Thaian N. Ton | Art Unit 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 117-127* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continuation of Disposition of Claims: Claims pending in the application are 1,2,7,16,50,52,63,65,70-72,78-80,85,88,98,102,109,115 and 117-127.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 7,16,50,52,63,65,70-72,78-80,85,88,98,102,109 and 115.

## DETAILED ACTION

Applicants' Amendment, filed 8/9/02, Paper No. 16, has been entered. Claim 1 has been amended.

Claims 1, 2, 7, 16, 50, 52, 63, 65, 70-72, 78-80, 85, 88, 98, 102, 109, 115 and 117-127 are pending.

Claims 1, 2, 117-127 are under current examination.

Any rejection made of record in the prior Office action, mailed 5/16/02, Paper No. 15, and not made of record in the instant Office action, has been withdrawn in view of Applicants amendments to the claims.

### *Specification*

The objection to the specification with regard to an embedded hyperlink and/or other form of browser-executable code is withdrawn in view of Applicants' Amendment to the specification.

### *Claim Rejections - 35 USC § 112*

The prior rejection of claims 1, 2 and 117-120 and 127 under 35 U.S.C. 112, 1st paragraph, for written description, is withdrawn in view of Applicants' Amendment(s) and/or arguments.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2 and 117-127 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, 1st paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at p. 1404 that,

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

The claims are broadly drawn to methods of diagnosing a disorder characterized by expression of a human cancer associated antigen precursor coded for by a nucleic acid molecule, comprising: contacting a biological sample isolated from a subject with an agent that binds under stringent hybridization conditions to the nucleic acid molecule, an expression product thereof, or a fragment of an

expression product thereof complexed with an HLA molecule, wherein the nucleic acid molecule is selected from the group consisting of (a) nucleic acid molecules which hybridize under stringent conditions to a molecule consisting of a nucleic acid sequence selected from the group consisting of SEQ ID Nos: 3-17 and which code for a cancer associated antigen precursor, (b) nucleic acid molecules that differ from the nucleic acid molecules of (a) in codon sequence due to the degeneracy of the genetic code, and (c) complements of (a) or (b), and determining the presence or level of interaction between the agent and nucleic acid molecule or the expression product as a determination of the disorder.

The specification teaches the isolation of eight gene products from the small cell lung cancer [SCLC] cell line [SEQ ID Nos: 3-10] and the isolation of 10 genes from the SCLC line SK-LC-13 [SEQ ID NOs: 3, 5, 6, 8, 11-17]. The specification provides teaching for the percentages of each of the clones [see Table 1a and 1b]. The specification teaches that Z1C2 [SEQ ID NO: 5] gene expression was analyzed by RT-PCR, and it was found that in normal tissues, ZIC2 mRNA was detectable in the brain and to a lesser extent testis, but it was not found in skin, kidney and small intestine. Further, the specification teaches that among tumor tissues, ZIC2 mRNA expression was found in varying degrees of expression in melanoma, colon cancer, breast cancer, heat and neck cancer, lunch cancer, transitional cancer, leiomyosarcoma and synovial sarcoma [see Table 2 and Example 3]. The specification teaches that SOX Group B family gene expression was analyzed by

Northern blot. It was found that SOX2 [SEQ ID NO: 3] expression was detected in brain, testis, and prostate and at lower levels in the small intestine and colon of normal tissues, but SOX2 expression was not found in the heart, placenta, lung, liver, skeletal muscle, kidney, pancreas, spleen, thymus, ovary and peripheral blood leukocytes. SOX1 [SEQ ID NO: 4], SOX3 [SEQ ID NO: 11] and SOX21 [SEQ ID NO: 12] mRNA was not detected in normal adult tissues. [See Example 4].

Stevanovic teaches the cDNA sequence of SOX2 which is 100% identical to SEQ ID NO: 3 of the instant application for the first 500 base pairs [see attached alignment]. Malas teaches the cloning and mapping of the human SOX1 gene, which is 100% identical to SEQ ID NO: 4 of the instant application for the first 500 base pairs [see attached alignment]. Brown *et al.* teach the mRNA sequence of the human ZIC2 protein which is 100% identical to SEQ ID NO: 5 of the instant application for the first 500 base pairs [see attached alignment]. Kiesling teach the sequence of human Id4 which is 100% identical to SEQ ID NO: 6 of the instant application for the first 500 base pairs [see attached alignment]. Bossone *et al.* teach the sequence of MAZ which is 100% identical to SEQ ID NO: 7 of the instant application for the first 500 base pairs [see attached alignment]. Westendorf teach the mRNA sequence of mpp11, which is 100% identical to SEQ ID NO: 8 of the instant application for the first 500 base pairs [see attached alignment]. Asuru *et al.* teach the cloning and characterization of the human eukaryotic initiation factor 2B which is 100% identical to SEQ ID NO: 9 of the instant application for the first

500 base pairs [see attached alignment]. Amakawa *et al.* teach the mRNA sequence of human recombination signal binding protein [RBP] which is 100% identical to SEQ ID NO: 10 of the instant application for the first 500 base pairs [see attached alignment]. Stevanovic teaches the sequence of the human SOX3 gene, which is 100% identical to SEQ ID NO: 11 of the instant application for the first 500 base pairs [see attached alignment]. Malas *et al.* teach the sequence of the human SOX21 gene, which is 100% identical to SEQ ID NO: 12 of the instant application for the first 500 base pairs [see attached alignment]. Nagase *et al.* teach the human mRNA sequence for KIAA0963 protein, which is 100% identical to SEQ ID NO: 13 of the instant application for the first 500 base pairs [see attached alignment]. Triebel teach the mRNA sequence for the human LAG-3 gene, which is 100% identical to SEQ ID NO: 14 of the instant application for the first 500 base pairs [see attached alignment]. Koehrer *et al.* teach the human mRNA sequence for the clone DKFZp434C196 which is 99.8% identical to SEQ ID NOs: 15 and 16 of the instant application for the first 500 base pairs [see attached alignments]. However, the above citations do not specifically teach using SEQ ID NOS: 3-17 in methods of diagnosing a disorder characterized by the expression of a human cancer associated antigen precursor.

Neither the specification nor the art teach the skilled artisan how to use the invention as broadly claimed. The specification and claims of the instant application assert that under stringent hybridization conditions, an agent that

binds to the nucleic acid molecule [SEQ ID Nos: 3-17] allows for the diagnosis of any disorder. However, it is noted that the specification provides teachings with regard to SOX1 [SEQ ID NO: 4], SOX3 [SEQ ID NO: 11] and SOX21 [SEQ ID NO: 12], which was not expressed in normal tissues, SOX2 [SEQ ID NO: 3] expression which was detected in brain, testis, and prostate and at lower levels in the small intestine and colon of normal tissues, and Z1C2 [SEQ ID NO: 5] expression, which was the brain and to a lesser extent, testis. The specification does not provide teachings or guidance with regard to the expression of SEQ ID NO: 6-10, 13-17 in normal tissues, as the specification only teaches the isolation of these sequences from a small cell lung cancer cell line [see Table 1b, for example], nor does the specification provide teachings for the expression of these genes in tumors. The claims as broadly written, read on any type of disorder, however, the specification only provides teachings with regard to the isolation of these genes from SCLC cell lines. The specification does not provide sufficient teachings with regard to the expression [or lack thereof] for the sequences for the breadth claimed, such that one skilled in the art would be able to diagnose a disorder based upon the hybridization of a sample from a subject with an agent that binds it under stringent hybridization conditions because some of the sequences claimed are also expressed in normal tissue. There is no indication in the specification of a threshold which would be indicative of any disorder, as broadly claimed. Furthermore, because some of the claimed sequences are expressed in normal tissues [SEQ ID NO: 3 and 5],

distinguishing a tissue with a disorder from normal tissue solely based on sample expression would be unpredictable. The claims state that the presence or level of interaction between the agent and nucleic acid molecule are indicative of the determination of the disorder [see claim 1]. However, because some of the sequences would be expressed in normal tissues as well, it is unclear what level, or presence of an interaction would be required to differentiate between the expression of the gene in normal tissues versus tissues characterized by any particular disorder. While one could conduct additional experimentation to determine whether, e.g., expression of any of the SEQ ID Nos: 3-17, at certain levels might be associated with, e.g., certain types of cancer [SCLC, non-small cell lung cancer, melanoma, etc], the outcome of such research cannot be predicted and such further research and experimentation are both unpredictable and undue.

Furthermore, the teachings of the prior art do not provide evidence of how to use the methods of diagnosing any disorder, as broadly claimed, by contacting a biological sample isolated from a subject with an agent that binds under stringent hybridization conditions to the nucleic acid molecule, wherein the nucleic acid molecule is selected from the group consisting of SEQ ID Nos: 3-17. The teachings of the specification do not establish that one could actually detect expression of any of SEQ ID Nos: 3-17 by hybridization such that one could diagnose any disorder, as broadly claimed. Rather, the specification teaches that some of SEQ ID Nos [SEQ ID NO: 3 and 5] are expressed in normal tissue types, that SOX1 [SEQ ID NO: 4],

SOX3 [SEQ ID NO: 11] and SOX21 [SEQ ID NO: 12] are not expressed in normal tissues, but expressed in SCLC cell lines, and the specification does not provide teachings or guidance with regard to SEQ ID NO: 6-10, 13-17 [see *supra*]. In the absence of guidance from the specification, one of skill in the art may look to the teachings of the prior art for enablement of the claimed invention. However, the closest prior art references [see *supra*] do not provide support for the use of SEQ ID NOS: 3-17 expression for diagnosis of any disorder. As such, it is unpredictable as to whether one could successfully use the claimed invention, and accordingly, it would require undue experimentation for the skilled artisan to use the claimed invention.

*Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2 and 117-127 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, as written, is unclear. The claim recites "an agent that binds under stringent hybridization conditions to the nucleic acid molecule, an expression product thereof, or a fragment of an expression product thereof ..." in lines 4-5 of the claim. It is unclear how an agent would bind under stringent hybridization

conditions to an expression product or fragment of the expression product, as the expression product could be, for example, a peptide.

The claim is further unclear because it recites, "nucleic acid molecules which hybridize under stringent conditions to a molecule consisting of a nucleic acid sequence selected from the group consisting of SEQ ID Nos: 3-17 and which code for a cancer-associated antigen precursor" [see lines 6-9 of the claim]. It is unclear what codes for a "cancer-associated antigen precursor" – the nucleic acid which hybridize to the sequence, or the nucleic acid sequences SEQ ID Nos: 3-17? The claim is further unclear because it recites (1) and then followed by (b) and (c). It is suggested that (1) be written to recite (a). Claims 2, 117-127 depend from claim 1.

*Conclusion*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to Patsy Zimmerman, Patent Analyst, at (703) 305-2758. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-8724.

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